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Titration, an essential method for determining content in the modern laboratory

Dr. Jürgen Peters
SI-Analytics GmbH, Hattenbergstr. 10 55122 Mainz

The history

There were alchemistic methods of titration even more than 200 years ago. Because the chemicals and reagents are mixed together, color changes are interpreted as oracle and soothsayers along with alchemists clad in colorful garb spoke in clever patter, distributing uncertainty with double meanings and the feeling that everything powerful is complicated and still runs incorrectly! The only one who was running around wrong here were the "chemical technicians" who could document with his colorful lab coat that he missed the lab coat wash day. Perhaps also progress in the development of analytical chemistry and the state-of-the-art for analytical devices. Because what began 200 years ago and evolved to become the standard method of determining content in analysis, was still complicated and difficult to perform for non-technicians just 20 years ago. In 1773, George Fleischer said: "You shouldn't advise every person to use entirely concealed science and art: Among the thousands, only one can hardly achieve it because they don't know what they are looking for and where to find it. They believe each subject sends you their scheme, and instructs you through false terms, to vain universals and particulars, to bemuse their thoughts, that they cannot recognize nature."

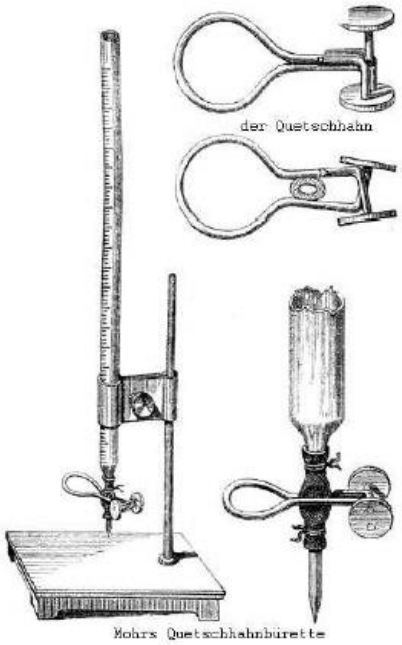

Figure 1: Mohr's pinch cock burette ["Meyers Konversations-Lexikon" [Meyers Conversational Dictionary] 1885–1890, 4th edition]

Over 200 years later, the situation has changed significantly. Whereas Mohr in the 18th century titrated using the simplest of burettes (Fig. 1), up until the 1960s, various more comfortable burettes were used up to the pellet burette. To produce a precise glass burette was still a challenge with the options available then. Nowadays, automatic titrators, burettes or bottle fixture burettes easily perform the same work with reproducible results. The tolerance of the diameter of a modern glass piston in a titrator is a maximum of three thousandths of a millimeter! Why this expense? One thing hasn't changed in over 200 years - the unit of measure of titration is and remains consumption in ml. The higher it is, the more reason to evaluate per Gay Lussac, who in 1830 could titrate the silver content in a coin with the existing glass burettes at a precision of 0.05%.

That knowledge has multiplied until now and many points of this theory are now standard knowledge in basic chemistry education (Fig. 2). The theory developed a broad basis in the 1920s and 1930s, with which modern students can always enjoy dabbling in. The technical development from the 1960s then led to the current titrators, which in principle consist of a measuring device and an integrated burette. Connection to a computer or an integrated computer has become a given nowadays (Fig. 3).

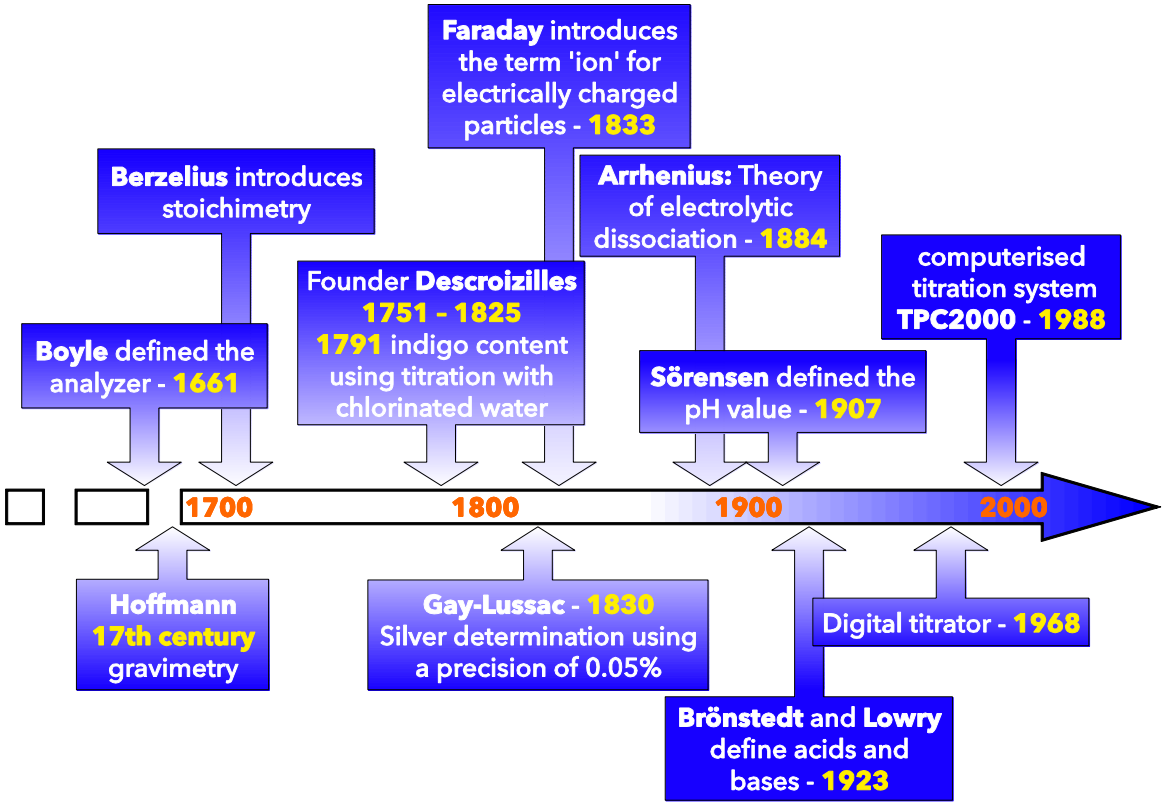

Figure 2: Development of titration

Figure 3: Modern titration system

The most important properties
The definition of titration has remained the same today:
1. A chemical reaction with the following requirements:
    - Clear stoichiometric relationships
    - Fast
    - Quantitative
    - Clear
    - Reproducible
2. A titration solution or a titration media is needed that is stable, is manufactured in a defined concentration and is simple to dose.
3. The end of the reaction or the point at which the unknown quantity of a sample is equivalent to the known quantity of the titration media, must be visible by the indication.

If a titration method is validated nowadays, these features are rechecked individually. It can occur that a titration method is used that results in uncertainties due to its stoichiometric conversion, such as was the case for many years in determining water using the Karl Fischer method. It shows that the reproducibility is often sufficient to develop a titration method. In general, stoichiometry can be fulfilled clearly and with all other features. This makes titration an "absolute method," which can be traced back to the chemical conversion without special calibration or adjustment. In addition to the simple implementation and widely available knowledge of titration, the numerous methods are a particular advantage that contributes to the broad use in today's labs.

Uses and examples
Titration today is used in all areas of analysis and is part of practically all areas of application and standards, some of which are listed below:

DIN EN ISO	Deutsche	EPA
ASTM	Einheitsverfahren [German	ILAC
BS	Uniform Methods]	European Medication Book
ANSI	DGF	US Pharmacopeia
NSSN	§ 64 LFGB	OSHA
WNNS	FDA	AOCS
ETS	ICH	
IEC	NIST	

If specific methods were added for individual branches, the list would continue endlessly.

There are many different sensors used here. Many applications work with glass electrodes as well as aqueous and non-aqueous solutions. Silver electrodes, such as for determining chloride in foods and many other applications, are widely used. All cheese eaters should be thankful because if the chloride content is too low, the cheese won't last; if it's too high, then the cheese is not enjoyable! Platinum electrodes or for dead stop titrations, double-platinum electrodes, are used for redox titrations. For ion-sensitive electrodes, there are numerous applications such as water hardness or determining the content of metals. The conductive electrodes can be used in many applications, but can be missed in selectivity. This plays no role if only the reaction heat is an issue, for which the temperature change is used to detect the chemical reaction and the equivalent conversion with the titration media. The nice color changes in the indicators are hardly observed in the lab now. Nowadays, they are evaluated objectively with photorodes, but have less use because potentiometric indication options are multi-functional and economically comparable.

In the pharmacy industry, many of the content determinations are titration methods. This mostly involves nitrogen bases from which many have hydrochloride. In modern times, a series of these bases are titrated indirectly through the adsorbed hydrochloride with soda lye. Here, for each Mol base, there must be one Mol HCl. In order to ensure this, the HCl is supplied in the excess. With the titration of soda lye, the excess is titrated first, then the adsorbed HCl is titrated with its largest pKs value in the second step. Figure 4 shows the titration of lidocaine hydrochloride with soda lye as an example.

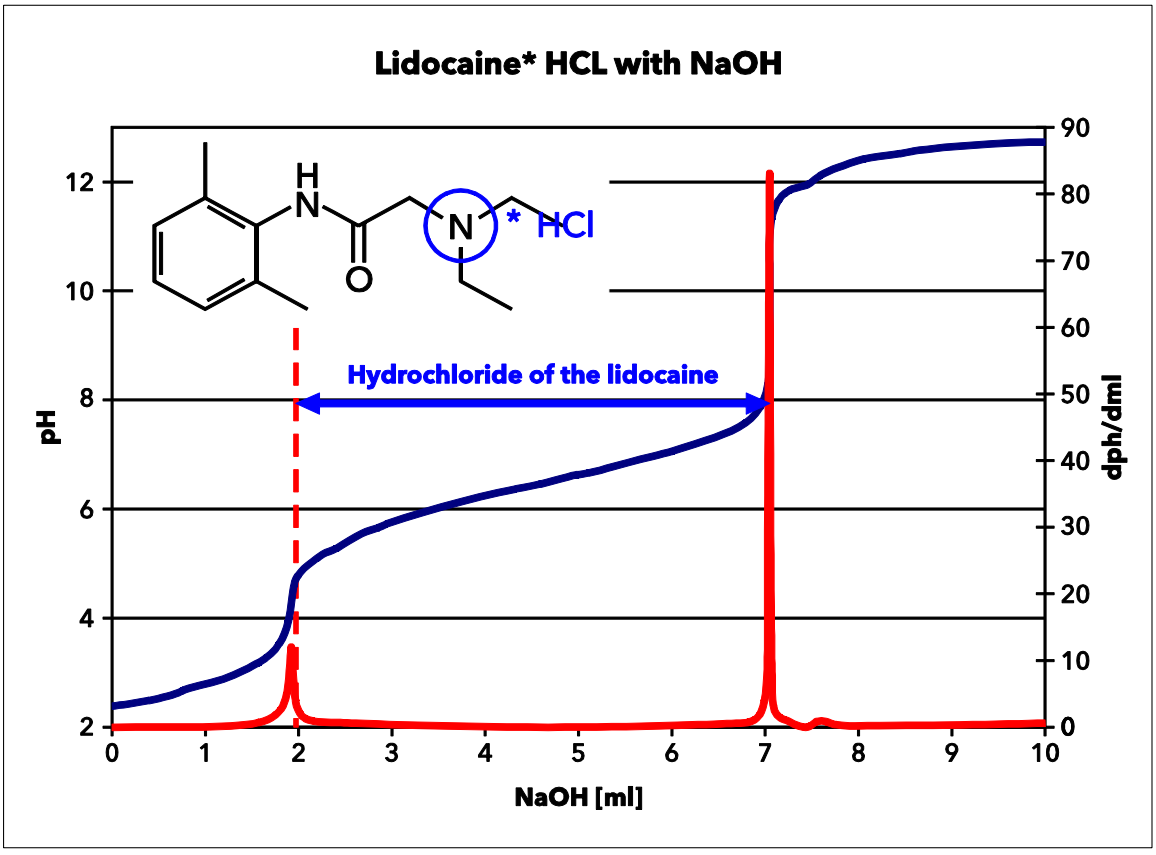

Figure 4: Titration curve of lidocaine hydrochloride with soda lye

Titration and "precision"

Since the measured unit of titration is volume, this must be determined as precisely as possible. The most required precision is defined in EN DIN ISO 8655 Part 3. There is, for example, a systematic error of 0.2% of the total volume of the cylinder and an additional error of 0.7% accepted for a 20 ml cylinder. The systematic error is thus the difference of the determined volume for the set volume; the additional error in essence is the standard deviation of the measuring method. Part 6 of the standard describes the gravimetric test with water. Water is dosed to a scale, at 10%, 50% and 100% of the cylinder volume. Of course, the temperature and air pressure are taken into account. The manufacturer's specifications are more precise and in practice, the target "precisions" are even higher.

Then of course, "precision" is dependent on other parameters and also on the type of use. Titration methods are thus validated and the measurement uncertainty of the method is calculated in order to be able to make a statement about the result certainty. A titration method begins with the exact determination of content of the titration reagent, the "titer setting". Generally, a reference material is used with a certified content. The reference materials are usually traced to an NIST standard. In earlier times, the titer was determined based on a general specification such as, "Take approx. 200 mg weighed precisely to four digits and run x titrations and enter in the mean for the titer". This method has the disadvantage that only one point of the relation of weight and result are available for all possible sample amounts.

Nowadays, mostly different weigh-ins are used and added in a line. The weigh-in is added to the x axis and the use is added to the y axis (Fig. 5). With this type of representation, the quality of the lines in the form of the correlation coefficients or the determination measurement and also the intersection with the y axis can be evaluated along with the mean value and the standard deviation. Both sets of information are important quality features of the titer setting method and give a reliable overview of the correct functionality of titrator and application.

Titer setting NaOH 0.1 mol/L

No.	Weight [g]	Consumption [mol/L]	Titer
1	0,1189	5,8445	1,0060
2	0,1576	7,7489	1,0057
3	0,2090	10,2722	1,0061
4	0,2578	12,6710	1,0061
5	0,3045	14,9631	1,0063
		Mean	1,0060
		RSD [%]	0,0195

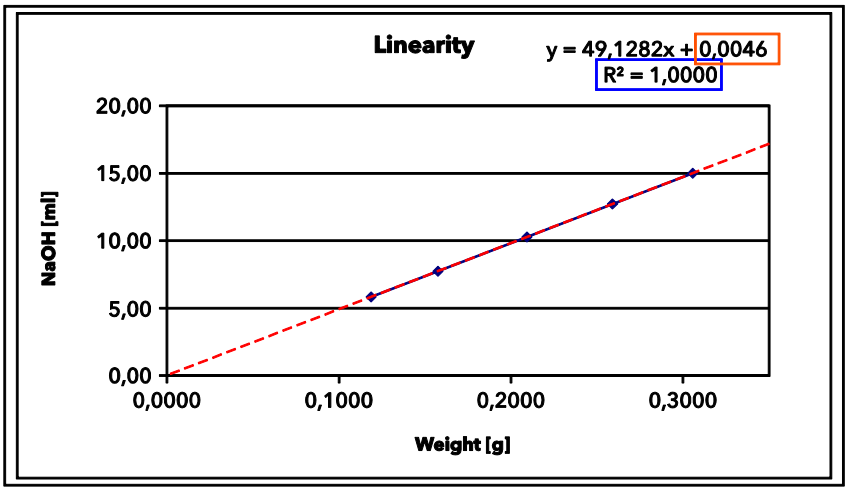

Figure 5: Titer setting of soda lye with potassium hydrogen phthalate

Figure 5 shows five titrations for the titer setting of a soda lye 0.1 mol/l in tabular form and a graphic. The table contains the titer mean value from five titrations and the relative standard deviation. The titer is within the anticipated range and the relative standard deviation shows very good reproducibility. The evaluation of the line of best fit shows additional information, namely, perfect linearity in the form of stability index R2 = 1,0000 (outlined in blue). An even more important figure is the zero crossing of the y axis. It means consumption without a standard being weighed in. In this example, the value 0.0046 ml (framed in orange) and is so small that it has practically no relevance. If the value is greater than a "drop" with approx. 0.05 ml, that could be a tip toward a blind value that must be determined with a separate titration. A negative "blind value" is not possible; this could cause an error in the sample measuring. In this way, many errors and problems in a titration method can be easily detected and avoided. Consumption in this example lies between 5 and 15 ml for a modern titrator (in this case, 20 ml cylinder), which is a good volume for a titration. This example shows a "precision" as the sum of systematic and additional errors that is still better than the result from Gay Lussac in 1830 when determining the silver in silver coins. This cannot be assumed for all applications; the values can deviate from the part considerably sometimes. The "precision" is determined to validate a method or to calculate the determination of uncertainties.

Summary

The example of titer setting clearly shows that the focus in the titration application has diverged from the simple glass burette, with which an experienced "lab tech" could produce highly precise results, to highly precise automated titrators. The steps for validating the method and the titrator using the titer up to the analysis result and it reproducibility are quantified today and it is truly simple to produce precise analysis with a tabular calculation. Thus, highly precise titration results are no longer the goal today for the special talents of lab techs. The analysis result has become more reliable; the accuracy is traceable through validation and largely independent of the operator. The uncertainty of a titration method can be quantified prior to implementation due to the individual analysis steps. Thus, the certainty of the statement about a precise content increases in a specific sample.

The development of the analysis method has not yet been completed even after 200 years, which calls to mind the passage: In 1875, the director of the American patent office submitted his resignation and suggested the office be closed because in his opinion, there was nothing more to be invented [David Louis, Wussten sie schon, dass? [Did you already know that?], Heyne book no. 4673 (Printed 1977].

Author:
Dr. Jürgen Peters
Titration Application
SI Analytics GmbH
Hattenbergstraße 10
55122 Mainz
Telefon: (0 61 31)66-50 62
Telefax: (0 61 31)66-50 01 juergen.peters@xyleminc.com www.si-analytics.com